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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,979	10/01/2003	Limin Li	5398-001-27	6296

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EXAMINER	
PENG, BO	
ART UNIT	**PAPER NUMBER**
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,979	LI, LIMIN	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 27-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/14/06;8/25/04*. 12/16/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction election

1. The Office acknowledges the receipt of Applicant's election, filed on November 13, 2006. Applicant elects Group III, Claims 20-26, with traverse.

2. The traverse is on the ground(s) that the search and examination of all currently pending claims would not post an undue burden on the examiner because a search for the antibody would be expected to uncover art potentially relevant to the claims in any of Group 1-VI.

3. Applicant's arguments are considered but found not persuasive for following reasons: Groups I-VI are different methods. Methods of reducing viral budding from a mammalian cell, treating infection by an enveloped virus in a subject using TSG 101 antibody, and delivering a therapeutic molecule to a mammalian cell using TSG 101 antibody conjugated to a therapeutic molecule differ from each other with respect to systems, such as *in vitro*, *in vivo* or *ex vivo*, compositions/ingredients, method steps, and endpoints. Therefore, each method is patentably distinct. The search and examination of more than one unrelated invention constitute an undue burden on the Office. The requirement is still deemed proper and is therefore made FINAL.

4. Accordingly, Claims 1-50 are pending. Claims 1-19 and 27-50 are withdrawn as non-elected. Claims 20-26 are under consideration in this Office action.

Information Disclosure Statement

5. The information disclosure statement submitted on February 14, 2006, is compliant with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. An initialed and dated copy of Applicant's IDS form 1449 is

attached to the instant Office action.

6. The information disclosure statements filed on August 25, 2004, fail to completely comply with 37 CFR 1.98(b)(5) because they lack titles of the publications listed under other documents (See MPEP 609). The information referred to therein has not been considered. The US and foreign patent documents have been considered.

Claim Rejections - 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 20-26 are directed to a method for treating infection by an enveloped virus in a mammal, comprising administering to said mammal a therapeutically effective amount of an antibody, wherein said antibody binds a TSG101 protein, whereby said enveloped virus infection is treated, wherein said antibody binds the N-terminal or C-terminal region of said TSG101 protein, wherein said mammal is a human, wherein said antibody binds an epitope comprised in the amino acid region selected from the group consisting of VRETVNVITLYKDLKPVL (SEQ ID NO:2) and QLRALMQKARKTAGLSDLY (SEQ ID NO:3), wherein said enveloped virus is selected from the group consisting of human immunodeficiency virus type I (HIV-I), human immunodeficiency virus type II (HIV-II), Marburg virus, and Ebola virus, wherein said antibody is a monoclonal antibody, wherein the method of Claim 20, further comprises administering to said mammal a therapeutically effective amount of one or more other therapeutic agents.

9. Claims 20-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)).

10. *Nature of the invention.* The claims are drawn to a method for treating infection by an enveloped virus in a mammal, including humans, using an antibody against cellular protein TSG101.

11. *Breadth of the claims.* The claims are broad, encompassing treatment of all viral infections caused by all enveloped viruses in any mammals.

12. *State of the prior art.* At the time the invention was made, it was known in the art that some enveloped viruses, like HIV-1, Ebola, etc., utilize cellular protein TSG101, to bud from cells (Martin-Serrano, 2001, cited in IDS). The PPxY, YxxL and PTAP motif in viral proteins and the UEV domain of Tsg101 are involved in the interaction between the virus proteins and TSG101 (Pornillos et al., 2002, cited in IDS; VerPlank et al., 2001, cited in IDS). Based on the insight into the molecular mechanism underlying the process of viral budding in HIV-infected cells, it is hypothesized or suggested that blocking TSG101 could prevent HIV-1 budding (Senior, 2001).

13. It is also known in the art, however, that a successful antibody therapy for treating viral infection *in vivo* is not routinely achievable by those skilled in the art. Most trials of antibody therapy for treating viral infection, such as for HAV, HBV and HIV infection, have been shown to have no treatment benefit, (Keller, 2000, Table 1, p. 603). For example, passive transfer of human neutralizing antibodies for treating HIV infection only resulted in delayed HIV rebound,

thus failing to treat the HIV infection (Trkola et al 2005). The prior art describes a number of concerns pertaining to the development of antibody therapy for treating HIV infection, such as effectiveness of antibody against the virus, and maintaining an effective concentration of the antibody *in vivo* (Trkola, see Discussion, p. 618-620).

13. *Predictability of the art.* The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). The prior art has described that most antibody therapy for treating viral infections provides no benefit (Keller, Table 1, p. 603), due to lack of effective antibodies and other obstacles to maintain an effective concentration of antibody in vivo, failing to compete with viral replication. Therefore, it is unpredictable in the art if the alleged method of treating viral infection using antibody against TSG101 can overcome these obstacles to successful antibody therapy, resulting in treatment benefit.

14. The specification has disclosed that antibodies against N- and C- termini of TSG101 can inhibit 50-70% MLV production in N2a cells (see FIG. 2 and [0018]). The specification has also disclosed that anti-TSG101 "E" can result in more than 70% inhibition of HIV-1 virion release in 293 cells (FIG.6), and about 60% inhibition of TSG101 in H9 cells at 80 ug/mL concentration (FIG. 7). Applicant also shows that polyclonal anti-TSG101 antibodies can partially (about 55%) inhibit the release of Ebola virus into Hela cells (Paragraph [0195], Figure 15). No *in vivo* testing was done. Thus, given the partial inhibiting effect of virus infection in *in vitro* assays, Applicant has not proven how this partial inhibition of HIV or Ebola *in vitro* by anti-TGS101 antibodies can result in clinical benefit *in vivo*, particularly when the other partially un-inhibited viruses can continue to replicate *in vivo*.

15. *Working examples and Guidance in the specification.* The specification disclosed some working examples of inhibiting MLV, HIV and Ebola production in *in vitro* assays. Only partial inhibiting effect was observed in these testing. No *in vivo* testing was done. The specification does not disclose the effect, if any, that anti-TSG101 antibodies can have on virus replication in any mammals.

16. Although the specification refers generally to some methods of producing antibodies against TSG101 pharmaceutical formulation and administration, the specification provides little guidance regarding a method to overcome the obstacles facing antibody therapy in general, like how to increase the effectiveness of antibodies against TSG101 *in vivo.*

17. *Amount of experimentation necessary.* It would require extensive research to develop a method of treating a viral infection in mammals including humans using anti-TSG101. Applicant had made some anti-TSG101 antibodies that have been shown to partially inhibit MLV, HIV or Ebola in *in vitro* assays, but has not shown that anti-TSG101 antibodies can effectively block viral production either *in vitro* or *in vivo.* One would require engaging an undue amount of experimentation in order to evaluate if the anti-TSG101 antibody has a therapeutic effect *in vivo,* and develop an effective antibody therapy to treat viral infections caused by all enveloped viruses in mammals. Essentially, the Applicant has left to others all of the work required to ultimately develop a method for treating infection by an enveloped virus in a mammal using anti-TSG101 antibody.

18. For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods. Thus, the instant invention, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, lacks an enabling disclosure.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that forms the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

20. Claims 20-22 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Zavitz (US2004/0109861A).

21. Claims 20-22 and 25 are directed to a method for treating infection by an enveloped virus in a mammal, comprising administering to said mammal a therapeutically effective amount of an antibody, wherein said antibody binds a TSG101 protein, whereby said enveloped virus infection is treated, wherein said antibody binds the N-terminal or C-terminal region of said TSG101 protein, wherein said enveloped virus is selected from the group consisting of human immunodeficiency virus type I (HIV-I), human immunodeficiency virus type II (HIV-II), Marburg virus, and Ebola virus, wherein said antibody is a monoclonal antibody, wherein the method of Claim 20, further comprises administering to said mammal a therapeutically effective amount of one or more other therapeutic agents.

22. Zavitz teaches a method of treating HIV infection comprising administering antibody to cells or tissue *in vitro* or in a patient (see Paragraph [0241] and [0242]). The antibody

administered may be immunoreactive with Tsg101 or HIV GAG or GAGp6. Suitable antibodies may be monoclonal or polyclonal, or single-chain antibodies. Zavitz teaches that an antibody specific to the UEV domain of TSG101 is administered to cells or tissue *in vitro* or in a patient.

23. Since Zavitz's antibody therapy for treating HIV infection using anti-TSG101 antibody meets the limitation of the instant method described in Claims 20-22 and 25, the instant claims 20-22 and 15 are anticipated by Zavitz.

Remarks

24. No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

BP
Bo Peng, Ph.D.
2/15/07

Bruce Campell
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